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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,388	03/26/2004	Gerry Shaw	5853-400	8619

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EXAMINER	
GUCKER, STEPHEN	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
05/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,388	SHAW ET AL.	
	Examiner	Art Unit	
	STEPHEN GUCKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 6-12* is/are pending in the application.

4a) Of the above claim(s) *7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/12/07 has been entered.

2. Claims 7-10 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/14/07.

3. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3, 6, and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. The instant specification discloses that the ELISA capture assay of the present invention can reliably detect NF-H in small 50µl volumes in quantities as low as 50pg (equivalent to 1ng/ml or 1µg/L, see figure 1). The disclosure does not teach a detection capability of 1pg/µl *per se*, because 1pg/µl is below the detection limits of the assay *unless* a 50µl sample is used which would raise the level of NF-H in the sample to 50pg, the smallest amount that the assay can detect. This is a new matter rejection.

7. Claims 1, 3, 6, and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant specification discloses that the ELISA capture assay of the present invention can reliably detect NF-H in small 50µl volumes in quantities as low as 50pg (equivalent to 1ng/ml or 1µg/L, see figure 1). The disclosure does not teach a detection capability of 1pg/µl *per se*, because 1pg/µl is below the detection limits of the assay *unless* a 50µl sample is used which would raise the level of NF-H in the sample to 50pg, the smallest amount that the assay can detect. Because the specification teaches that the smallest amount of NF-H that can be detected by the present invention is 50pg, detection of amounts below this level is not enabled.

8. Claims 1, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zelman. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a

background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Hu (March 8, 2002) teaches a method of detecting neuronal injury in subjects with Alzheimer's disease (AD) and vascular dementia by using ELISA with antibodies that bind NF-H found in CSF samples taken from the subjects (abstract, Figures 2-3). Hu does not teach using blood samples. Zelman teaches a method of detecting neuronal injury in subjects by using ELISA with antibodies that bind neurofilament proteins found in blood samples taken from the subjects (abstract and column 3, line 25 to column 4, line 42). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the methods of Hu with the blood samples of Zelman because it is simpler and easier to procure a blood sample and assay it by ELISA than it is to procure a CSF sample by lumbar puncture because the blood sample can be simply taken from the arm (no usual side effects) while the CSF sample needs to be taken from the spinal cord region with the attendant risks of damaging the cord and then producing the side effects usually resulting from lumbar puncture such as headaches. The instant invention is *prima facie* obvious because the artisan would be motivated to take a simple venous blood sample (less time consuming than even a routine blood donation) than take a riskier CSF sample from the spinal cord region.

Applicant's arguments filed 12/12/07 have been fully considered but they are not persuasive because Applicant argues that Zelman is not enabling and that at the time of the invention one would not have known that NF-H could be detected in blood, serum or plasma from an injured mammal and used as a marker for neuronal injury, and that this was an unexpected result. However, Zelman discloses this unexpected result of finding large proteins migrating from the CSF into the bloodstream of injured or diseased patients:

It would not be expected that cleaved-tau levels would also be elevated in serum in these patients as blood is compartmentalized from CSF by the blood-brain-barrier. The fundamental basis for compartmentalization between blood and CSF is the tight junctions that exist between endothelial cells that comprise the blood-brain-barrier (Saunders NR, Habgood MD and Dziegielewska. (1999) Barrier mechanisms in the brain, I. Adult brain. Clin. Exp. Pharmacol. Physiol. 26: 11-19). These tight junctions exclude all but the smallest proteins (less than 5 kDa molecular weight). As cleaved-tau is much larger, demonstrating an average molecular weight of 40 kDa, one skilled-in-the-art would not expect to find cleaved-tau in serum of these patients. Surprisingly, when we examined patients undergoing neuronal degeneration resulting from sever head injury or stroke, we found elevated levels of serum cleaved-tau in both groups of patients (Table 2). The cause of this unexpected elevation in both CSF and serum cleaved-tau is unknown, however, the elevation in serum cleaved-tau may be related to disruption of the blood-brain-barrier that is disease-associated. (column 14, lines 41-61).

Therefore, given Zelman's disclosure and working example that tau protein from the CSF could "leak" into and be detected in the bloodstream of patients at levels ranging from 0.14 - 4.56ng/ml (equivalent to 0.14 – 4.56pg/µl, see Table 2), it would have been obvious to look for NF-H as well, because Zelman suggests it. See especially column 3, lines 51-56; column 5, line 50 to column 6, line 11; column 21, lines 9-22; and Table 2. The expectation of

success is provided by Hu because of the working examples of detecting neuronal injury in subjects with Alzheimer's disease (AD) and vascular dementia by using ELISA with antibodies that bind NF-H in CSF samples. Given Zelman's disclosure and direct suggestion to detect NF-H in blood, it would have at least been obvious to try to use the methods of Hu on blood samples. Therefore, in addition to the invention being obvious to succeed for the reasons already of record, the combined references also make the invention obvious to try because all the claimed elements (the axonal proteins (tau, NF-L, NF-M, and NF-H), the process steps of detection, the patient population, and the disorders) were known in the prior art from a finite number of choices and one skilled in the art could have combined the elements as claimed by known methods of detection such as ELISA with no change in their respective functions (the NF-H was known to increase in CSF from neurological disorders, it was known it could be detected by ELISA, and other large neuronal proteins from degenerating axons were now known to be found in blood, so it was no longer an unexpected result), and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

9. Claims 1, 3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zelman as applied above, and further in view of Grainger et al. (US 5,595,722; "Grainger"). Grainger discloses that chicken polyclonal antibodies are suitable to be used in ELISAs to routinely detect and assay proteins such as TGF-β in serum and plasma samples (Example 8). Therefore, the use of chicken polyclonal antibodies in combination with the previously applied art would have yielded predictable results to one of ordinary skill in the

art at the time of the invention, absent evidence to the contrary. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

10. Claims 1, 3, 6, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. ("Hu") in view of Zelman as applied above, and further in view of Posmantur et al. (IDS filed 1/30/06; "Postmantur"). Posmantur discloses that NF-H levels in the brain begin to decrease as soon as 3 hours post-injury (pages 539-540). Therefore, it would be obvious to try to look for the missing NF-H protein from the brain in the blood within a few hours of a neuronal injury as taught by Postmantur with the methods disclosed by Hu and Zelman, and the combination with the previously applied art would have yielded predictable results to one of ordinary skill in the art at the time of the invention, absent evidence to the contrary. See KSR Int'l Co. v. Telefex Inc., 127 S. Ct. 1727 (U.S. 2007).

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. G./

Examiner, Art Unit 1649

Stephen Gucker

May 29, 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649